REMARKS

Reconsideration of this application is respectfully requested. The Office Action dated February 27, 2003 had been preceded by an Office Action dated February 25, 2003. In a telephone conversation, the Examiner indicated that the later Office Action was a substitute Office Action, and that a bona fide attempt to respond thereto would be regarded as responsive.

In the Office Action, at page 2, section 2, the Examiner acknowledge Applicants' priority claim, but stated that the provisional application upon which the claim was based did not provide a utility for the claimed invention. Applicants respectfully disagree; the provisional application set forth a specific, substantial and credible utility, for the same reasons discussed herein. Accordingly, Applicants are entitled to the priority date of the earliest filed provisional application, namely May 25, 1999.

The Examiner also objected to the specification because of several alleged informalities. Applicants have amended the specification to add sequence identifiers to the sequences discussed by the Examiner, as well as to another sequence identified by Applicants; a new Sequence Listing is submitted herewith. Applicants have also capitalized trademarks and added accompanying generic language where such did not already exist. Applicants respectfully submit that no new matter is added hereby, and request that the objections be withdrawn.

Rejections under 35 U.S.C. § 101

Claims 1-10 were rejected under 35 U.S.C. § 101 for allegedly lacking utility. The Examiner asserts that a specific and substantial utility is one that is particular to the subject matter claimed and that identifies a "real world" use, and recites Brenner v. Manson 148 USPQ 689 (1966). Applicants traverse the rejection.

According to the Examiner, a utility such as chromosomal localization would apply to every naturally occurring polynucleotide and is therefore not specific. Applicants respectfully submit that not every naturally occurring polynucleotide would map to the 2q11-12 region of chromosome 2. Moreover, if the standard for specificity were that apparently utilized by the Examiner (namely, that all naturally-occurring polynucleotides hybridize to some chromosome somewhere and therefore chromosomal localization is not a specific utility), novel antibodies would be unpatentable for lack of utility because all antibodies bind to some antigen somewhere. Applicants respectfully submit that requirement for a specific utility does not mean that such utility must be unique.

The U.S. Court of Appeals for the Federal Circuit has stated: "An invention need not be the best or the only way to accomplish a certain result, and it need only be useful to some extent and in certain applications." *Carl Zeiss Stiftung v. Renishaw plc*, 20 U.S.P.Q.2d 1094, 1100 (1991). Therefore, Applicants' claimed nucleic acids do not need to be the best or only way to identify human chromosome 2, to analyze abnormalities associated with gene mapping to chromosome 2, to distinguish conditions in which this marker is rearranged or deleted, or to serve as a positional marker to map other genes of unknown location. Rather, the claimed nucleic acids need only be useful to some extent and in certain applications. Applicants respectfully submit that the claimed nucleic acids fulfill this requirement.

Claims 1 through 3 recite isolated nucleic acids comprising all or a portion of SEQ ID NO:1 and nucleic acids that hybridize to SEQ ID NO:1 and are at least 98% identical to SEQ ID NO:2. Support for this amendment is found in the specification, in the paragraph spanning pages 6 and 7. Applicants' specification asserts a specific utility for the claimed nucleic acids, namely, their use by those skilled in the art in well-known

techniques to analyze abnormalities associated with gene mapping to chromosome 2 (enabling one to distinguish conditions in which this marker is rearranged or deleted), and additionally as a positional marker to map other genes of unknown location (specification, page 27, lines 23 through 27). These utilities are specific, substantial, and credible.

The presently claimed nucleic acids can be used to detect human chromosome 2 and rearrangements or deletions associated with chromosome 2, for example, in fluorescence *in situ* hybridization (FISH) studies (and other methods used in the real world of genetic analysis). Such uses are credible "real world" utilities that can be practiced with Applicants' invention without need for any additional research, and are exemplified in Exhibits 1 through 6.

Giardino et al. (Exhibit 1) analyzed a chromosomal rearrangement in a patient with psychotic illness and mild mental retardation. Giardino et al., at 319, col. 2, last full ¶. FISH was used to characterize a small supernumerary marker chromosome (SMC) found in the cells of the mother and child. *Id.* at 321, Fig 2. Giardino et al. determined that the SMC was derived from the proximal region of human chromosome 2. *Id.* at 321, Table 1. Several probes for 2q11.2 and 2q12 detected both the normal chromosomes and the SMC, whereas more distal probes for 2q12 detected only the normal chromosomes. *Id.* Thus, probes mapping to the proximal region of chromosome 2 are useful for determining the presence of normal chromosome 2 sequences and for characterizing the composition of the SMC. Since Applicant's DNA localizes to the proximal region of chromosome 2, it is useful as a probe for determining the presence of normal chromosome 2 sequences and for characterizing the composition of the SMC described by Giardino et al.

Moreover, in Table 2, Giardino et al. provide a list of chromosome 2 partial trisomy cases and associated phenotypic findings. All of the trisomy cases appear to be associated with the proximal region of chromosome 2, which is the region to which Applicants mapped IL-1 eta DNA. Applicants asserted that IL-1 eta DNA can be used to detect human chromosome 2 and rearrangements or deletions associated with chromosome 2. (Specification at 27, lines 23-27.) The Office has not provided any reason to doubt that Applicants' DNA could be used to detect and characterize these cases of trisomy of the proximal chromosome 2 region. Such a use is a "real world" use.

As stated in Giardino et al., "FISH analyses using unique sequences are useful means of obtaining information about the euchromatic regions contained in a SMC and delineating new chromosomal syndromes, aimed to offer suitable genetic counseling, especially when an SMC is observed in prenatal diagnosis." Giardino et al. at 322, col. 2, first ¶. There can be no doubt that Applicants' unique DNA sequence would be useful in FISH analyses for obtaining information about the euchromatic regions contained in a SMC and delineating new chromosomal syndromes.

Riegel et al. (Exhibit 2) examined a patient with various abnormalities, and found an abnormal chromosome 2. Riegel et al. at 76, Abstract. Using FISH, they determined that there was a direct tandem duplication of 2q11-q13.2. *Id.* Several probes for 2q11.1-q13 detected a single signal on one chromosome and two signals on the abnormal chromosome. *Id.* at 78, Table 1. In contrast, a probe for 2q14 detected a single signal on both chromosomes. *Id.* Thus, probes mapping to the proximal region of chromosome 2 are useful for determining the presence of normal chromosome 2 sequences and for characterizing the composition of the abnormal chromosome. Since Applicants' DNA localizes to the proximal region of chromosome 2, it is useful as a probe for determining

the presence of normal chromosome 2 sequences and for characterizing the duplicated region of chromosome 2 described by Riegel et al.

Riegel et al. indicate that the duplication was "identified with the help of fluorescence in situ hybridization studies using band-specific YAC probes." *Id.* at 76, col. 1-2, bridging ¶. Applicant asserted that IL-1 eta DNA can be used to detect human chromosome 2 and rearrangements or deletions associated with chromosome 2. (Specification at 27, lines 23-27.) The Office has not provided any reason to doubt that Applicants' DNA could be used to detect and characterize duplications of the proximal chromosome 2 region as described in Riegel et al. Such a use is a "real world" use.

Wang et al. (Exhibit 3) examined a fetus with various abnormalities, and found an abnormal chromosome 2. Wang et al. at 312, Abstract. Using FISH, they determined that there was a triplication of 2q11.2-q21. *Id.* Thus, probes mapping to the proximal region of chromosome 2 are useful for determining the presence of normal chromosome 2 sequences and for characterizing the composition of the abnormal chromosome containing the triplication. Since Applicants' DNA localizes to the proximal region of chromosome 2, it is useful as a probe for determining the presence of normal chromosome 2 sequences and for characterizing the triplicated region of chromosome 2 described by Wang et al. Such a use is a "real world" use.

Glass et al. (Exhibit 4) examined a patient with various abnormalities, and found an abnormal chromosome 2. Glass et al. at 319, Abstract. Using FISH, they determined that there was a proximal 2q trisomy (2q11.2-q21.1). *Id.* FISH showed an insertion of chromosome 2-derived material into the middle of the short arm of chromosome 8. *Id.* at 320, Figure 4. Since Applicants' DNA localizes to the proximal region of chromosome 2, it is useful as a probe for determining the presence of normal chromosome 2 sequences

and for characterizing the insertion of material derived from chromosome 2 into chromosome 8 described by Glass et al. Such a use is a "real world" use.

Mu et al. (Exhibit 5) examined a patient with various abnormalities, and found an abnormal chromosome 2. Mu et al. at 57, Summary. They determined that there was a tandem duplication of 2q11.2-q14.2. *Id.* *Id.* at 78, Table 1. Although Mu et al. did not perform any hybridization analyses, probes mapping to the proximal region of chromosome 2 would have been useful for determining the presence of normal chromosome 2 sequences on one of the chromosomes and for characterizing the duplicated region of the abnormal chromosome. Since Applicants' DNA localizes to the proximal region of chromosome 2, it is useful as a probe for determining the presence of normal chromosome 2 sequences and for characterizing the duplicated region of chromosome 2 described by Mu et al. Such a use is a "real world" use.

Reddy et al. (Exhibit 6) studied intrachromosomal triplications, including a triplication of 2q11.2-2q21. Reddy et al. at 134, Abstract. Reddy et al. states: "Triplications can be mistaken for duplications. Therefore, in assessing duplications, FISH confirmation is recommended." *Id.* Consequently, it is appreciated in the art that FISH is useful for assessing duplications and confirming triplications, including those involving the proximal region of chromosome 2. Since the presently claimed DNA localizes to the proximal region of chromosome 2, it is useful as a probe for determining the presence of normal chromosome 2 sequences and for assessing duplications and confirming triplications involving the proximal region of chromosome 2. Such a use is a "real world" use.

Exhibits 1 through 6 provide evidence that, as Applicants asserted in the specification, the claimed nucleic acids can be used to identify human chromosome 2 and to distinguish conditions in which this marker is rearranged or deleted. In view of this

evidence, it is indisputable that Applicants' claimed nucleic acids are useful at least "to some extent and in certain applications," which is sufficient to fulfill the utility requirement of 35 U.S.C. § 101. *See Carl Zeiss Stiftung v. Renishaw plc*, 20 U.S.P.Q.2d at 1100. Accordingly, Applicant respectfully requests withdrawal of the rejection.

Furthermore, Applicants' claims recite expression vectors comprising the aforementioned nucleic acids; host cells comprising the expression vectors; and methods for producing polypeptides by culturing these host cells. The polypeptides obtainable by using the invention represented by these claims have numerous uses, as set forth in the instant specification on pages 28 through 33. Such uses include protein purification, identification or purification of cells that bind IL-1 eta, as carriers for delivery of agents to such cells, and as research tools. Moreover, IL-1 eta polypeptides have utility as immunogens in the development of antibodies, especially antibodies that can be used to distinguish between IL-1 family members and in clarifying the roles(s) of IL-1 family members in the inflammatory response.

Those of ordinary skill in the art would recognize the use of a new IL-1 family member as a research tool in studying other members of the IL-1 family, as well as in the development of antibodies that are useful to distinguish between members of the IL-1 family. As the Examiner correctly noted, both IL-1 alpha and IL-1 beta are proinflammatory cytokines, and IL-1 receptor antagonist is an antagonist thereof. However, while the Examiner apparently relies on the statement in Dinarello et al. that IL-18 is not an endogenous pyrogen to conclude that therefore IL-18 is not involved in inflammation, Applicants respectfully submit, that like the aforementioned cytokines, IL-18 is involved in modulating the inflammatory response.

At page 6, Dinarello characterize IL-18 (also known as Interferon Gamma inducing factor, or IGIF) as a generally proinflammatory cytokine. They go on to

summarize what was then known about signal transduction pathway for IL-18, which appears to utilize several signaling molecules known to be involved in the inflammatory process, including IL-1 receptor-associated kinase (IRAK) and tumor necrosis factor receptor associated protein 6 (TRAF-6). They also note that IL-18 is a potent inducer of tumor necrosis factor and interferon gamma as well as chemokines, further demonstrating its contribution to inflammation. Thus, the IL-1 family members discussed in Dinarello et al. are involved in controlling the inflammatory response, either upregulating it in the case of the agonists IL-1 alpha, IL-1 beta and IL-18, or downregulating it in the case of IL-1 receptor antagonist.

Both upregulating and downregulating are critical to a successful inflammatory response, and clarifying the role of various family members (including any organ or tissue-specific effects) is a necessary step in developing effective therapeutic agents in this area. Those of skill in the art are aware of the role(s) of members of the IL-1 family in the immune and inflammatory responses and would find Applicants teaching of the use of IL-1 eta to study IL-1 mediated processes, to protect against infection, and to stimulate the immune system, as well as use of inhibitors as anti-inflammatory agents to be "real world" (e.g., specific and substantial) uses.

As discussed above, Applicants' specification asserts numerous credible "real world" utilities. Applicants have provided herewith Exhibits 1 through 6, which provide objective evidence supporting Applicants' asserted utilities. The Office has provided no evidence to the contrary. Accordingly, Applicant respectfully requests withdrawal of the rejection.

Rejections under 35 U.S.C. § 112, first paragraph

Claims 1 through 10 were rejected under 35 U.S.C. § 112, first paragraph, for allegedly not having either a specific and substantial asserted utility or a well established utility for the same reasons set forth for the rejections under 35 U.S.C. § 101, and thus the specification allegedly does not teach one of ordinary skill in the art how to use the invention.

Applicants traverse the rejection. For the reasons detailed above, the claimed invention does indeed have a specific, substantial and creditable utility, and the skilled artisan would readily understand how to use it. Accordingly, Applicants respectfully requests withdrawal of the rejection.

Claims 1, 4, 7 and 10 were further rejected under 35 U.S.C. § 112, first paragraph, because the specification allegedly does not reasonably provide enablement for nucleic acids encoding variants or fragments of the polypeptide of SEQ ID NO:2. Applicants respectfully disagree; having taught the nucleotide and amino acid sequence of IL-1 eta, Applicants have enabled one of ordinary skill in the art in molecular biology to make a plethora of fragments and variants thereof and test them for activity by the application of routine experimentation. However, Applicants have amended the claims to recite nucleic acids comprising the polynucleotide of SEQ ID NO:1 and nucleic acids that hybridize thereto and are at least 98% identical to SEQ ID NO:1. Applicants respectfully submit that disclosure of the species of SEQ ID NO:1 enables the genus of nucleic acids presently claimed.

Moreover, Applicants point out that claims 1 and 2 are not limited to nucleic acids that encode a polypeptide that binds to an IL-1 family member. Rather, the claims encompass nucleic acids without regard to the ability of any encoded polypeptide to bind

to a receptor. Consequently, none of the Office's reasons for non-enablement are relevant to claims 1 and 2. Accordingly, Applicant respectfully requests withdrawal of the rejection.

Claims 1, 4, 7 and 10 were also rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter not described in the specification in such a way as to convey to one of skill in the art that Applicants had, at the time the application was filed, possession of the claimed invention. Applicants respectfully disagree; having taught the nucleotide and amino acid sequence of IL-1 eta and numerous variants and fragments thereof, Applicants have described a genus of IL-1 eta nucleic acids in such a way as to convey possession thereof to one of ordinary skill in the art in molecular biology. However, Applicants have amended the claims to recite nucleic acids comprising the polynucleotide of SEQ ID NO:1 and nucleic acids that hybridize thereto and are at least 98% identical to SEQ ID NO:1. Applicants respectfully submit that disclosure of the species of SEQ ID NO:1 and the variants disused in the specification, particularly at pages 5 through 10, describes the genus of nucleic acids presently claimed.

Claims 1, 4, 7 and 10 were rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite in the use of the phrase "polypeptides of the invention." Applicants respectfully disagree; the specification does provide a particular definition of the "polypeptides of the invention." However, claims 1, 4, 7 and 10 have been amended and no longer include this phrase. Accordingly, this rejection is moot, and Applicants request that it be withdrawn.

Rejections under 35 U.S.C. § 102

Claims 1, 4, 7 and 10 were rejected under 35 U.S.C. § 102(a) and 35 U.S.C. § 102(e) as allegedly being anticipated by Burgess et al., WO 01/40291, June 7, 2001. According to the Examiner, Burgess et al. teach a sequence that encodes a protein that is identical to amino acids 9 through 157 of the presently claimed invention and is 95% homologous overall. Applicants respectfully assert that they are entitled to their original priority date, namely May 25, 1999, inasmuch as the provisional application filed on that date disclosed the presently claimed invention and provided a specific, substantial and credible utility therefore. Thus, Applicants respectfully assert that Burgess et al. is not available as prior art with respect to the presently claimed nucleic acids. Moreover, Applicants have amended claim 1 to recite the nucleic acid of SEQ ID NO:1 and DNA capable of hybridizing thereto that is at least 98% identical to SEQ ID NO:1. Applicants respectfully assert that Burgess et al. do not teach (or even suggest) the presently claimed nucleic acids; accordingly, Applicants request that the rejection be withdrawn.

Claims 1 through 10 were rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Smith et al., *J. Biol. Chem.* 275(2):1169, nominal publication date January 14, 2000. According to the Examiner, Smith et al. teach a sequence that is identical to that presently claimed. Applicants respectfully assert that they are entitled to their original priority date, namely May 25, 1999, inasmuch as the provisional application filed on that date disclosed the presently claimed invention and provided a specific, substantial and credible utility therefore. Applicants respectfully assert that Smith et al. is not available as prior art with respect to the presently claimed nucleic acids; accordingly, Applicants request that the rejection be withdrawn.

Claims 1, 4, 7 and 10 were rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Young et al., U.S Patent 5,943,310, August 31, 1999, and European patent application EP 0 879 889 A2. According to the Examiner, Young et al. teaches a sequences that encodes a polypeptide whose first 88 amino acids are identical to instant SEQ ID NO:2. The Examiner further alleges that the polynucleotide of Young et al. would hybridize to the complement of SEQ ID NO:1 under moderately stringent conditions. Applicants have amended claim 1 to recite the nucleic acid of SEQ ID NO:1 and DNA capable of hybridizing thereto under stringent conditions and that is at least 98% identical to SEQ ID NO:1. Applicants respectfully assert that Young et al. do not teach (or even suggest) the presently claimed nucleic acids; accordingly, Applicants request that the rejection be withdrawn.

Claims 1, 4, 7 and 10 were rejected under 35 U.S.C. § 102 (e) as allegedly being anticipated by Burgess et al., U.S. Patent application 2002/0068279 A1 (priority date December 6, 1999). According to the Examiner, this Burgess et al. reference teaches the same sequence taught by WO 01/41291, which encodes a protein that is identical to amino acids 9 through 157 of the presently claimed invention and is 95% homologous overall. Applicants respectfully assert that they are entitled to their original priority date, namely May 25, 1999, inasmuch as the provisional application filed on that date disclosed the presently claimed invention and provided a specific, substantial and credible utility therefore. Applicants respectfully assert that Burgess et al. is not available as prior art with respect to the presently claimed nucleic acids. Moreover, Applicants have amended claim 1 to recite the nucleic acid of SEQ ID NO:1 and DNA capable of hybridizing thereto that is at least 98% identical to SEQ ID NO:1. Applicants respectfully assert that

Burgess et al. do not teach (or even suggest) the presently claimed nucleic acids; accordingly, Applicants request that the rejection be withdrawn.

CONCLUSIONS

1 through 10 are now pending in the application and are believed to be in condition for allowance. If the examiner has any questions or concerns about the present claims, she is asked to contact the undersigned at the direct dial number given below, to facilitate prosecution and speed allowance of the claims.

Respectfully submitted,

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